AUTOMATED SPINE SURVEY ITERATIVE SCAN TECHNIQUE (ASSIST)

Cross Reference to Related Applications

[0001] The present application claims the benefit of the U.S. Provisional Patent Application Ser. No. 60/552,332, filed 11 March 2004, the disclosure of which is hereby incorporated by reference in its entirety.

Field of the Invention

[0002] The present invention relates, in general, to medical diagnostic imaging devices that perform scout scans for localization and autoprescription.

Background of the Invention

[0003] Diagnostic imaging of the spine of a patient is often useful for identifying disease or an injury to the spine itself or as a readily locatable landmark for other tissues. Unfortunately, human error may occur due to the variability in the patient population or due to an oversight. The mistake may arise in incorrectly labeling vertebrae and discs in a diagnostic image. The mistake may arise in incorrectly visually identifying the corresponding vertebrae under the skin before performing a surgical or therapeutic (e.g., radiation) treatment. The mistake may arise in improperly identifying a normal, benign, or malignant condition because an opportunity is missed to correctly correlate information from a plurality of imaging systems (e.g., a type of tissue may be determined if an MRI and a CT image could be properly correlated and analyzed).

[0004] With regard to spine prescription, a number of complications exist that necessitate having an extensively trained clinician identify the imaged vertebrae. For instance, the quality of the diagnostic image may vary depending on the source and type of imaging modality. The presented image volume provided may not include the top and bottom vertebrae. Vertebrae and discs may not be adequately captured in the image due to congenital defect, disease, injury or surgery. The individual in question may have an atypical number of mobile pre-

sacral vertebrae, either more or less than 23. Further, the spacing and curvature of the individual's spine may be rather exceptional.

[0005] Even if the vertebrae and discs may be accurately identified in the diagnostic image, it is often helpful to be able to obtain a one-to-one correspondence between the readily visible and markable skin/surface and underlying structures or pathology detectable by a variety of imaging modalities. This may facilitate clinical correlation, XRT, image guided biopsy or surgical exploration, multimodality or interstudy image fusion, motion correction/compensation, and 3D space tracking.

[0006] Current methods, (e.g. bath oil/vitamin E capsules for MRI), have several limitations including single image modality utility requiring completely different and sometimes incompatible devices for each modality, complicating the procedure and adding potential error in subsequent multimodality integration/fusion. They require a separate step to mark the skin/surface where the localizer is placed and when as commonly affixed to the skin by overlying tape, may artifactually indent/compress the soft tissue beneath the marker or allow the localizer to move, further adding to potential error. Sterile technique is often difficult to achieve. Furthermore, it may be impossible to discriminate point localizers from each other or directly attain surface coordinates and measurements with cross sectional imaging techniques. In regards to the latter, indirect instrument values are subject to significant error due to potential InterScan patient motion, nonorthogonal surface contours, and technique related aberrations which may not be appreciated as current multipurpose spatial reference phantoms are not designed for simultaneous patient imaging.

[0007] The trend is to take and digitally store lots of data on a patient, including MR and CT images. You want to both compare each patient's data to his/her own data, and "pools" of data from other people. Little problem: How do you make sense of pictures taken at different times, using different types of machines and different actual machines, for the same or different people? That's what Dr. Weiss accomplishes with his techniques for the skull: well-characterized fixed reference

points. He proposes something similar for the spine. Nothing "automatic" exists today and there are no real standards for how to characterize points of reference on the skull, let alone the spine.

[0008] Limited coverage, resolution and contrast of conventional MRI localizers coupled with a high prevalence of spinal variance make definitive numbering difficult and may contribute to the risk of spinal intervention at the wrong level. Only 20% of the population exhibit the classic 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal grouping. For instance, 2-11% of individuals have a cephlad or caudal shift of lumbar-sacral transition, respectively resulting in 23 or 25 rather than the typical 24 mobile presacral vertebrae. Numbering difficulties are often heightened in patients referred for spine MRI. Such patients are more likely than the general population to have anomalies, acquired pathology, or instrumentation that distorts the appearance of vertebrae and discs. Moreover, these patients are often unable to lie still within the magnet for more than a short period of time due to a high prevalence of back pain and spasms. Resultant intrascan motion confounds image interpretation and interscan motion renders scan coordinates and positional references unreliable.

[0009] While data remains somewhat limited, various authors report an approximately 2-5% incidence of wrong level approach spinal intervention, with most cases involving the lower lumbar interspaces. Such surgical misadventures may lead to needless pain and suffering, as well as contribute to accelerating medical malpractice costs. The first multi-million dollar jury verdict for such a wrong level approach was awarded in 2002.

[0010] Although several research techniques have been described to automate spine image analysis, to the authors' best knowledge, none has successfully addressed the need for accurate and unambiguous numbering. Computer characterization of a vertebrae or disc is of limited clinical value if that structure can not be accurately identified and named.

[0011] Consequently, a significant need exists for an improved approach to localizing and autoprescribing through multi-modal quick scans of the brain and/or spine.

Furthermore, there is a need for enhancing personal medicine with a method of aligning skull and spine images.

[0012] Once one image set is autoprescribed, it would be further beneficial to correlate with other types of imaging modalities that are also autoprescribed. One advantage is that calculations of changes over time for the same patient may quickly identify injury or disease. Another advantage is that different spectral emissions illicit different information about a tissue. Correlating between a plurality of imaging modalities, if a common tissue structure can be localized for each, may enable autodiagnosis as to whether the tissue is normal, benign or malignant. Consequently, it would be of a further advantage to extend spine autoprescription across multiple sources of diagnostic images.

Brief Summary of the Invention

[0013] The present invention addresses these and other problems in the prior art by providing an apparatus and method of localizing a spinal column of a patient with robust automated labeling of vertebrae across a population and across different imaging modalities facilitating autoprescription and follow-on therapeutic procedures. Thereby, human error in incorrectly identifying a vertebrae in an image, and thus mislocating a surgical site, is avoided.

[0014] In one aspect of the invention, an apparatus processed a medical diagnostic image of a patient's torso by identifying voxels of appropriate size to be putative spinal structures. Then disc constraints are applied to identify a long chain of spinal structures that are then labeled.

[0015] In another aspect of the invention, this processing is in conjunction with a localized coil placed on the torso of the patient that provides an external reference correlated to the identification and labeling, enabling accurate insertion or aiming of therapeutic treatments.

[0016] By virtue of the foregoing, an entire spine can be effectively surveyed with sub-millimeter in–plane resolution MRI in less than one minute. All cervical-thoracic-lumbar vertebrae and discs can be readily identified and definitively

numbered by visual inspection. All cervical-thoracic-lumbar vertebrae and discs can be readily identified and definitively numbered by semi-automated computer algorithm. Rapid technique should facilitate accurate vertebral numbering, improve patient care, and reduce the risk of surgical misadventure. Coupled with an integrated head and spine array coil, rapid computer automated iterative prescription and analysis of the entire neuro-axis may be possible.

[0017] These and other objects and advantages of the present invention shall be made apparent from the accompanying drawings and the description thereof.

Brief Description of the Figures

[0018] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments of the invention, and, together with the general description of the invention given above, and the detailed description of the embodiments given below, serve to explain the principles of the present invention.

[0019] FIG. 1 is a diagram of an automated spinal diagnostic system.

[0020] FIG. 2 is a flow diagram of a spine identification sequence or operations or procedure for the automated spinal diagnostic system of FIG. 1.

[0021] FIG. 3 is a diagram of a projection function of adjacent objects (ϕ_p and ϕ_q represent the angles between the line connecting candidate disc p and q through their centroid and the major axis of disc p and q respectively, wherein $0<\phi_p<90^0$ and $\phi_p < 45^0$ and $\phi_p < 45^0$ let d_c be the value of d for any candidate disc in cervical-thoracic spine region and d_L in the thoracic-lumbar spine, then $6mm<d_c < 80$ mm and 8 mm $< d_L < 100$ mm.

[0022] FIG. 4 is a diagram of distance constraint chains with a cluster, k, is part of a disc chain if its closest superior neighbor has k as its closest inferior neighbor and k's closest inferior neighbor has (k) as its closest superior neighbor.

[0023] FIG. 5 is a 7-slice sagittal MRI projected image volume having a 35 cm FOV top half and FIG. 6 is a 35 cm FOV bottom half illustrating typical search regions wherein voxels exceeding intensity threshold are depicted with those meeting

additional disc constraints are highlighted as putative disks and connected by a curved line through their centroids.

[0024] FIG. 7 is a combined sagittal image depicting search paths parallel to the curved line of FIG. 6 connecting a centroid of a C2-3 disc with longest disc chains from top and bottom half images (FIGS.). Dots correspond to local maxima along these paths.

[0025] FIG. 8 is a sagittal image through the entire spine with all intervetebral discs auto-labeled with labeling of vertebrae omitted for clarity with three-dimensional (3-D) coordinates generated by an algorithm providing a means for discs or vertebral bodies to be labeled in any subsequent imaging plane providing no gross inter-scan patient movement.

[0026] FIG. 9 a sagittal image through the entire spine of a patient with 23 mobile/presacral vertebrae with correct auto-labeling of first 22 interspaces.

[0027] FIG. 10 a sagittal image through the entire spine of a patient with 25 potentially mobile presacral vertebrae with correct auto-labeling of the first 23 interspaces.

[0028] FIG. 11 a sagittal image through the entire spine of a patient with surgically fused L4-5 interspace and associated artifact from a metallic cage with correct labeling of all 23 interspaces including a good approximation of the L4-5 disc.

[0029] Fig 12 a sagittal image through the entire spine of a patient with vertebral planus of T-10 mislabeled due to a less robust disc discrimination process.

[0030] FIG. 13 is a sagittal image through the entire spine of the patient of FIG. 12 with correctly labeled vertebrae due to a more robust disc discrimination process including Gaussian filters.

[0031] FIGS. 14A-14I are diagrams of a point localizer; FIG. 14A depicts a frontal view of the point localizer affixed to fabric; FIG. 14B depicts a reverse side of the point localizer of FIG. 14A; FIG. 14C is a perspective view of the point localizer and underlying fabric affixed to the skin; FIG. 14D is an enface view of the fabric with corresponding marking affixed to the skin; FIG. 14E is an enface view of the

localizer affixed to skin; FIG. 14F is a diagram view of a port integrated into a tubular ring; FIG. 14G is a frontal view of a modified ring shaped localizer affixed to fabric with additional markings; FIG. 14H is a frontal view of the fabric in FIG. 14G with the localizer removed; FIG. 14I is a frontal view of a multilocalizer sheet demonstrating the adhesive backing and overlying fabric with localizers removed.

[0032] FIGS. 15A-15F illustrate a cross-shaped grid configuration; FIG. 15A is an enface view of the grid with modified square as the central hub and uniquely positioned rows of tubing radiating along the vertical and horizontal axes; FIG. 15B is a schematic of axial cross sections acquired at representative distances from the horizontal axis; FIG. 5C demonstrates the underlying marked fabric with the superimposed tubing in FIG. 15A removed; FIG. 15D is a variant of FIG. 15A with modified ring serving as a central hub; FIG. 15E depicts a limb fixation ring and angulation adjuster; and FIG. 15F depicts a radiopaque grid with underlying ruled fabric strips removed.

[0033] FIG. 16A is an enface view of the grid/phantom configuration with tubular lattice, overlying a diagonally oriented slice indicator, and underlying a partially adhesive fabric with markings and perforations; FIG. 16B is a schematic cross section of a representative axial section of the grid/phantom configuration of FIG. 16A.

[0034] FIGS. 17A-17B are diagrams of localizers in a packaged strip or roll, regularly spaced at 5 cm or other intervals.

[0035] FIGS. 18A-18B are a lattice localizer having tube diameters varied to identify unique locations.

[0036] FIGS. 19A-19D are depictions of a full-spin grid localizer and spinal coil.

Detailed Description of the Invention

Spine localization, automated labeling, and data fusion diagnostic system.

[0037] In FIG. 1, an automated spinal diagnostic system 10 includes a diagnostic imaging system 12 (e.g., MRI, CT) that is used to image a torso of a patient 14

that is advantageously covered by a skin/surface marking system 16 that serves as an integrated multimodality, multi-functional spatial reference. The diagnostic imaging system 12 may include scanning of the skull 18, the full spine 20, and pelvic bones 22. The diagnostic imaging system 12 serves as an automated MRI technique that rapidly surveys the entire spine providing accurate definitive numbering of all discs and vertebrae. In the particular illustrative version, the entire spine can be effectively surveyed with sub-millimeter in-plane resolution MRI in less than 1 minute. C-T-L vertebrae and discs can be readily identified and definitively numbered by visual inspection or semi-automated computer algorithm ("ASSIST").

[0038] Correctly identifying each vertebrae and disc in the spine 20 is complicated in certain instances when the skull 18 and/or the pelvic bones 22 are not imaged. In some instances, a vertebrae or disc (depending on whether CT or MRI is being used respectively) will fail to image properly, depicted at 24. In addition, the highly predominant number of twenty-three vertebrae may not be the case for certain individuals, such as twenty-four as depicted. Having the correct vertebrae references may be important in localizing a suspicious lesion 26, such as for a later therapeutic procedure, represented as a radiation device 28.

[0039] The diagnostic imaging system 12 may derive a sagittal image 28 of the torso 14 from a volume CT scan 30. Alternatively, the diagnostic imaging system 12 may produce an upper cervical-thoracic sagittal image 32 and a lower thoracic-lumbar sagittal image 34, such as from MRI. A spine autoimage processor 40, which may be a process hosted by the diagnostic imaging system 12 or by a remote device, performs a number of subprocesses to correctly identify and label the spine 20.

[0040] In an illustrative version of the diagnostic imaging system 12, MRI studies were performed on a clinical 1.5T magnet with standard 4-channel quadrature array 6-element spine coil and surface coil correction algorithm. Contiguous two-station 35 cm FOV sagittal FGRE sequences were pre-programmed, providing full cervical, thoracic and lumbar (C-T-L) spine coverage. Combined sagittal

FOV of 70 cm., 7 sections, L15-R15, 4 mm skip 1 mm; 512x352, 1 nex, TR 58, TE 2.0, 30° flip, BW 15.6; 21 sec x 2 stations = 42 sec. To facilitate and standardize auto-prescriptions, a line was drawn on the spine coil for the technologists to landmark (set as scanner's 0 coordinate) rather than have them use a superficial anatomic feature. The coil has a contoured head/neck rest assuring grossly similar positioning of the cranial-cervical junction of each patient relative to this landmark. The semi-automated disc detection and numbering algorithm of the spine image processor 40 was iteratively developed, tested and refined on batches of consecutive de-identified patient studies and results compared to neuroradiologist assignments. The spine image processor 40 was implemented in MATLAB 7.

[0041] In block 41, a computer algorithm is hosted on the spine image processor for the identification and labeling of disc and vertebrae from auto-prescribed sagittal MRI or sagittal auto-reformatted CT data, described in greater detail below. This information may be advantageously provided to an automated spine image analysis algorithm 43 that further characterizes each disc and/or vertebrae level. Alternatively or in addition, this information from block 41 may be advantageously provided to an auto-prescription algorithm 45 for additional image sequences, utilizing the identified spinal landmarks as references. Further, the additional processes 43, 45 may exchange information with each other, such as detained analysis and diagnosis of a particular vertebrae in block 43 being enabled by auto-prescribed detailed images in block 45.

[0042] These analyses performed by the spine image processor 40 in the illustrative version key upon one or more sources of information that identify the top vertebrae.

[0043] In particular, in block 46, a top vertebrae is identified, which may be automated in block 48 by interfacing with an automated cranium identification system, such as described in U.S. Pat. Appl. Ser. No. 10/803,700, "AUTOMATED BRAIN MRI AND CT PRESCRIPTIONS IN TALAIRACH SPACE" to Dr. Weiss, filed 18 March 2004, the disclosure of which is hereby

incorporated by reference in its entirety. Alternatively, logic may be incorporated into the spine image processor 40 wherein a spine algorithm in block 50 recognizes a top vertebrae. As a further alternative and as fall back option should automated means fail, in block 52 a technologist input is received to identify the top vertebrae.

[0044] The neuroradiologist could readily visualize and definitively number all C-T-L levels on ASSIST localizers. 6/50 patients had a congenital shift in lumbar-sacral transition; 3 with 23 mobile pre-sacral vertebrae and 3 with 25 mobile pre-sacral vertebraeBased upon usual of manual placement of a single seed in the C2-3 interspace for accurate identification and numbering of the other 22 discs, in the illustrative version with 50/50 cases performed by the spine autoprescription processor 40,. The automated disc detection and numbering algorithm was concordant with neuroradiologist assignments in 50/50 (100%) of cases.

[0045] With a labeled disc image 64, correct relative location to other imaged tissue of interest, depicted at 65 may be used for further diagnostic procedures or therapeutic intervention. For instance, in block 66 with an ability to correlate images taken with the same type of imaging modality at different times, growth progression of a suspicious lesion or changes due to an intervening injury may be compared between images. In addition, images taken with different imaging modalities may be cross referenced to perform multi-spectral diagnoses (block 68), wherein information on a type of tissue may be gained by its different responses to various types of electromagnetic spectra. With tissue diagnosis complete, in block 70 may correctly orient a therapeutic agent, such as the radiation device 28 or a guided minimally invasive surgical instrument (not shown). Alternatively, for an externally oriented procedure, a surgeon may reference either the relative location to a known spinal constituent (e.g., vertebrae) and/or reference the skin/surfacing marking system 16.

[0046] In an illustrative implementation of the spine image processor 40 of FIG. 1, Internal Review Board (IRB) approval for the research study was obtained. As part of a revised thoracic spine clinical MRI protocol instituted at an outpatient

imaging facility, patients received a rapid total spine ASSIST localizer with pre-set parameters. All studies were performed on a 1.5T GE Excite MRI system with standard 4-channel, 6-element quadrature spine coil and surface coil correction algorithm. Contiguous two-station 35 cm FOV sagittal FGRE sequences were pre-programmed, providing full cervical, thoracic and lumbar (C-T-L) spine coverage. Combined sagittal FOV was 70 cm., 7 sections obtained at each station, L15-R15, 4 mm skip 1 mm; 512x352,1 nex, TR 58, TE 2.0, 30° flip, BW 15.6; 21 sec x 2 stations = 42 sec. These ASSIST studies were de-identified in consecutive batches and copied to CD for subsequent off-line review, computer algorithm development and testing. A semi-automated disc detection and numbering algorithm was iteratively developed and results compared to neuroradiologist assignments.

[0047] The first batch of 27 cases was initially run with an algorithm 100 developed using previously obtained, non surface-coil corrected ASSIST images, The first step, we input cervicothoracic (top half), and thorariclumbar (bottom half) spines. A threshold and a median spatial filter are applied to the search region. Then, additional disc constraints are applied to identify longest chain in top and bottom images. Candidate discs must extend onto at least two adjacent slices. Objects at the boundary or touching the boundary of the search region are excluded. Different threshold values, and candidate discs' constraints are applied to the top, and bottom half image.

[0048] In FIG. 2, the automated disc detection and numbering algorithm 100 is a multi-step iterative process. DICOM (i.e., Digital Imaging and Communications in Medicine)ASSIST images of the cervicothoracic (top half), and thorarolumbar (bottom half) spine are first input into MATLAB 7 (The Math Works, Inc., Natick, MA) for digital image processing.

[0049] Initially, these two data sets are processed to obtain putative discs separately, utilizing different threshold values and disc constraint parameters (block 104), with resulting upper and lower images 106, 108 depicted in FIGS. 5 and 6 respectively. Image volumes 106, 108 are enhanced with a tophat filter and

background noise is suppressed. A posterior edge 110 of the back is then identified in each image 106, 108 and search regions 112, 114 assigned respectively. The algorithm 100 thresholds and applies a median spatial filter to the search regions. Voxels 116 exceeding threshold values are then subjected to additional constraints.

[0050] Acceptable voxels 120 must extend onto at least two adjacent sagittal sections but not touch the boundary of the search region 112, 114 . The acceptable voxels 116 must lie 6-80 mm in the cervicothoracic (C-T), and 8- 100 mm in the thoracolumbar (T-L) region from adjacent candidate voxels 120. The centroids of these voxel clusters 120 (candidate discs) are then connected by curved line 122. The angle subtended by the line 122 connecting the centroid of adjacent candidate discs 120 and the major axis of these discs 122 must be between 45^0 and 135^0 in both the C-T and T-L spine. In FIG. 3, projection analysis is used to constrain disc assignments. Furthermore, for a disc (k) to be considered part of a chain, its closest superior neighbor must have k as its closest inferior neighbor and k's closest inferior neighbor must have k as its closest superior neighbor. In FIG. 4, an angle relative to the major axis is evaluated to constrain disc assignments. The algorithm selects the longest disc chain (white discs connected by curved line) in the C-T and T-L regions respectively (FIGS. 5, 6).

[0051] In block 130, the technologist is instructed to approximate (click on) the centroid of C2-3 at anytime during or before the aforementioned candidate disc evaluation. The centroid of C2-3 and the longest disc chains in the C-T and T-L spines are connected with a straight line. Using 3D linear interpolation, the program searches along this line and twelve adjacent parallel lines 140, represented by only four in FIG. 7 for clarity due to their superimposition in the sagittal projection. After applying Gaussian filters, the algorithm 100 finds local intensity maxima along each path. Points 142 that are less than 7.5 mm apart are grouped into clusters. These clusters are analyzed based on orientation, eccentricity, and spatial relationship relative to other clusters (block 144 of FIG. 4).

[0052] Continuing with FIG. 2, if twenty-three (23) discs are selected in block 146, the computer auto-labels theses discs or adjacent vertebrae and stops (block 148), as depicted in FIG. 8. Otherwise, search criteria and thresholds are refined based on estimated inter-disc height (h) for each disc level (L) using the following formula: (equation 1) h = 0.6M for L= 1, 2, or 3 and h = M+(L-1.2)*0.05M for L>3. where M (mean) = distance along line thru centroids/23.

[0053] In block 150, if 23 discs are not yet identified in block 146, the program 100 extends the search line inferiorly based on the estimated position ($E_{x,y}$) of the missing disc(s).

$$E_{(x_j,y_j)} = (x_{j-1}, y_{j-1}) + h_a(x_{j-1}, y_{j-1}) \times \sum_{1}^{j-1} \frac{h_s(x,y)}{h_a(x,y)} \quad \text{(Equation 2)}$$

where ∂_a is the average vertebral height from a 22 subject training set, ∂_s is the vertebral height from the subject in question. The program searches for local maxima along this line extension and 24 adjacent parallel lines. A further determination is made in block 152 as to whether 23 discs have been found. Iteration continues as long as twenty-three (23) discs are not selected, as represented by block 154 that extends the search and the further determination of block 156, which labels the vertebrae is 23 are selected (block 157).

[0054] If not 23 discs in block 156, then in block 158 a further determination is then made that twenty-two (22) discs are selected. If so, the algorithm 100 will determine in block 160 whether the last identified level (L4-5) satisfies criteria for the terminal pre-sacral interspace suggesting a congenital variant with 23 rather than the typical 24 mobile presacral vertebrae (block 162). To be considered a terminal disc, the centroid of the 22nd disc must lie within 25% of its expected location (Ex, y) relative to the 21st disc. Additionally, the centroid must lie posterior to the centroid of the 21st disc and the slope of the 22nd disc must be positive and greater than that of the 21st disc.

[0055] If found in block 166, the discs are labeled in block 168. Else, if the terminal disc criteria are not met in block 166, the position of the 23rd (L5-S1) disc is estimated using Equation 2 (block 164), and search constraints refined. If the 23rd

disc is still not identified in block 166, the disc is presumed to be severely degenerated or post-surgical and the estimated position for L5-S1 will be accepted in block 170 and the discs thus labeled (block 172).

[0056] If less than 22 discs are identified by the algorithm in block 158, then the technologist will be instructed in block 174 to approximate (click on) the centroid of the last disc. The "combine data" step from block 144 is repeated and if necessary the "search for additional discs" step as well. If twenty-three (23) discs are selected in block 176, then the discs are labeled in block 178. Else, if twenty three (23) discs are still not selected in block 176, the algorithm prints out, "Sorry, computer unable to detect all the discs. Require technologist revision." (block 180)

[0057] The algorithm was run on an INTEL (San Jose, California) personal computer with a 2.8 Ghz Xeon processor. Computer auto-labeling was compared to independent neuroradiologist assignments for each patient's study. The automated spine MRI sequencing provided a robust survey of the entire C-T-L spine in 42 seconds total acquisition time. In all patients (50/50), the neuroradiologist could readily visualize and definitively number all C-T-L levels on the ASSIST localizers. These included six patients with a congenital shift in their lumbar-sacral transition; three with 23 mobile pre-sacral vertebrae (Fig 5) and three with 25 mobile pre-sacral vertebrae (Fig 6). Several patients had post-operative spines to include metallic instrumentation (Fig 7).

[0058] Automated disc detection/numbering: the initial algorithm tested on the first 27 surface-coil corrected studies was accurate in 26/27 cases (96%), the single error related to a severely collapsed vertebra (FIG. 12). The modified algorithm was accurate in all 50/50 cases (100%) of the patients to include the original 27 patients plus 23 subsequent cases, despite the presence of congenital variations (FIGS. 5, 6), post-operative changes (FIG. 11), and prominent disc or vertebral pathology (FIG. 13) in this patient population. None of the 50 cases required technologist input of more than a single interspace (C2-3) though the algorithm provides such an iterative pathway if necessary. In the vast majority of cases, the

algorithm 100, running on a personal computer with a 2.8 GHz processor, took less than 2 minutes to identify and label all intervertebral discs or vertebrae.

[0059] Although the ASSIST algorithm 100 was successful in all 50 patients studied, the 7 section sagittal acquisition would be expected to fail in subjects with severe scoliosis due to insufficient spine coverage. As such, if significant scoliosis is suspected, more sagittal sections could be auto-prescribed, the cost being a proportionate increase in scan time. The automated disc detection/numbering algorithm 100 was designed to accept any number of sagittal sections, however, its accuracy in patients with severe scoliosis is unknown and parameter modifications might be required. Additionally, ASSIST algorithm 100 was designed and tested only on an adult population. Consequently, the algorithm would likely require additional testing and modifications to perform optimally in the pediatric population.

[0060] While the illustrative disc detection algorithm 100 presently requires manual input of the most cephalad disc, C2-3, to achieve maximal accuracy, it should be appreciated that automated computer detection of this interspace may be implemented. The C2-3 disc may be readily discerned on midline sagittal head images with a 22-24 cm FOV (Weiss 2003, 2004) or ASSIST 35 cm FOV cervico-thoracic spine images based on several unique features. These include the characteristic shape of the C2 vertebrae and relatively constant relationship to the skull base and cervico-medullary junction.

[0061] Although the illustrative version is described for MRI, it should be appreciated that the ASSIST algorithm 100 has applications to other imaging platforms, such as CT, substituting automated sagittal CT spine reconstructions for the direct sagittal MRI acquisitions facilitating automated temporal comparisons, multi-modal multiparametric spinal analysis, and optimized intervention. As disclosed for MRI and CT of the brain in the cross-referenced application, direct scanner integration and related algorithms for computer assisted diagnosis could eventually enable "real-time" automated spine image analysis and iterative scan prescriptions.

[0062] For example, optimally angled axial oblique sequencing could be auto-prescribed through all interspaces or those discs demonstrating abnormal morphology or signal characteristics on the ASSIST or subsequent sagittal sequences. By streamlining and converting Matlab code to C++, algorithm processing time might be significantly shortened. Coupled with an integrated head and spine array coil, rapid computer automated iterative prescription and analysis of the entire neuro-axis may be possible.

[0063] In conclusion, the entire spine can be effectively surveyed with sub-millimeter in-plane resolution MRI in less than 1 minute. All C-T-L vertebrae and discs can be readily identified and definitively numbered by visual inspection or semi-automated computer algorithm. We advocate ASSIST for all thoracic and lumbar spine MRI studies. This rapid technique should facilitate accurate vertebral numbering, improve patient care, and reduce the risk of surgical misadventure.

Integrated Multimodality, Multi-Functional Spatial Reference and Skin/Surface Marking System.

[0064] With internal structures labeled, there are a number of advantages to providing an external skin/surface marking system. There are three major configurations of the device as follows: (1) a point localizer, (2) cross-shaped localizer grid, and (3) full planar localizer grid/phantom.

[0065] In one version, the point localizer 500 of FIGS. 14A-14I is a multimodality visible and compatible affixed to an adhesive fabric strip with corresponding markings so that after application and imaging the localizer can be removed with skin marking remaining. The localizer can also directly adhere to the skin. Alternatively, an ink or dye could be added to the adhesive/undersurface of the localizer to directly mark/imprint the skin obviating the fabric strip. For MRI and CT a small loop of tubing could be filled with a radioattenuative solution (e.g. containing iodine) doped with a paramagnetic relaxant (e.g. CuS04, MgS04, Gd-DTPA). Alternatively, the tubing itself may be radiopaque for optimal CT visualization. For nuclear imaging to include planar scintigraphy, SPECT and PET, a port would be included to allow filling with the appropriate radionuclide. While the above localizers would be visible with planar radiography, a fine wire

circle or dot (e.g. lead, aluminum) could be utilized with this modality given its very high spatial resolution. Other shapes and corresponding adhesive markings could be utilized to discriminate different foci and/or add further localizing capability. Additionally, an activatable chemiluminescent mixture could be added for thermography, optical imaging, light based 3D space tracking or simply improved visualization in a darkened environment.

[0066] In the second major configuration, a unique cross shaped grouping of prefilled or fillable tubing is utilized as a grid for cross sectional imaging with the number and position of tubes imaged in the axial or sagittal planes corresponding respectively to the slices z or y distance from the center. For planar radiography, a flexible radiopaque ruled cross shaped grid is employed. Both grids are removable from similarly ruled cross shaped adhesive strips after patient application and imaging.

[0067] Lastly, a unique essentially planar grid/phantom is described which may be of flexible construction and reversibly affixed to an adhesive/plastic sheet with corresponding grid pattern for skin marking and to serve as a sterile interface between patient and reusable grid/phantom. The grid/phantom may also be directly adherent to the skin for guided aspiration or biopsy with the cross sectionally resolvable spatial reference in place. A diagonally oriented prefilled or fillable tube overlies a grid like lattice of regularly spaced tubing so that slice location and thickness can be readily determined in the axial and sagittal planes. Additionally, the spatial accuracy of the imaging modality could be assessed and, if individual tubes are filled with different solutions, multipurpose references for MR/CT, and nuclear imaging could be achieved. Furthermore, if the tubing is surrounded by a perflurocarbon or other uniform substance without magnetic susceptibility, MR imaging could be improved by reducing skin/air susceptibility and motion artifact. Additionally, the grid/phantom could be incorporated in routinely utilized pads and binding devices with or without skin adhesion and marking.

[0068] Returning to the Drawings, FIGS. 14A-14I depict an illustrative version of a point localizer 500. In FIG. 14A, a loop of prefilled tubing 510 (i.e., a tubal lumen shaped into a tubal ring) is shown superimposed on and reversibly affixed to an underlying medical grade fabric 511, which may double as an adhesive bandage to both cover and mark a wound or puncture site. The diameter of the tubular ring 510 may be 2 cm mid luminal, as illustrated, or outer luminal, as perhaps preferable for integration with the cross shaped grid configuration. Other sized rings, to include in particular a 1 cm. diameter, may also have merit. The tubal lumen should measure 2-5 mm in cross sectional diameter. Cross sectional images through the ring will have characteristic and quantifiable appearances depending on slice thickness and distance from the center. A thin slice through the loop's center, for example, would demonstrate 2 circles of luminal diameter whose centers are separated by a distance equal to the ring's diameter.

[0069] The tube lumen can be filled with an appropriate concentration of an iodinated contrast agent for optimal CT visualization doped with a paramagnetic relaxant such as CuS04,MgS04, or GdDTPA to maximize MRI signal via preferential T1 shortening. Alternatively, the tubing itself may be optimally radiopaque for CT, obviating the iodinated contrast. If desired, for optical imaging, thermography, light based 3D space tracking, or improved visibility in a darkened environment, one could add an activatable chemiluminescent mixture whose critical reagents are separated by a membrane readily breached by external force applied to the ring.

[0070] A slightly redundant backing 512 is provided for the adhesive side of the fabric 51 to facilitate peeling (FIG. 14B arrows) and skin placement. With backing 512 removed, the unit 500 adheres to skin 513 as depicted in FIG. 14C. After imaging, the loop 510, which has its own adhesive undersurface, may be removed revealing an underlying fabric marking 514 as in FIG. 14D. The upper surface of the fabric, or circumscribed area thereof, may also have adhesive backing-like properties to facilitate detachment of the ring 510. Once separated from the fabric, the loop 510 could also directly adhere to the skin 513 as in FIG. 14E. Additionally, the adhesive undersurface of the ring could contain a medical

grade dye or ink so that a corresponding imprint would be left on the skin 513 after removal, potentially obviating the fabric marker.

[0071] A port 515 may be directly integrated into the tubular ring 510 as in FIG. 14F, and a vacuum created within the lumen to facilitate filling at the imaging center. This feature would be critical for radionuclide scans and add flexibility for other imaging studies.

[0072] To increase spatial reference capability and allow multiple localizers to be discriminated from each other, the ring and underlying fabric marking may be modified as in FIGS. 14G and 14H. As illustrated, two tubular spokes 516 at right angles to each other may be added with luminal diameter less than or equal to that of the loop. Typically, the modified ring would be positioned on the patient so that the spokes are aligned at 0 and 90 degrees as perhaps determined by the scanner's alignment light. Subsequent rings could be progressively rotated 90 degrees so that quadrants I, II, III, and IV are sequentially subserved by the spokes. With the simple ring included, this would provide 5 distinguishable localizers. Moreover, if stacking of two rings is utilized, 30 (5x6) distinguishable localizer configurations are possible. Suggested numbering would employ .the base 5 system, assigning the simple ring the value 0 and each modified ring the value of the quadrant subserved.

[0073] Multiple localizers may also be dispensed on a single sheet rather than individually packaged. FIG. 14I illustrates such a sheet, demonstrating adhesive backing 517 and overlying fabric 511 with the simple ring (left side) and modified ring (right side) localizers removed. Tabs 518 have been added to the fabric to facilitate both removal of the unit from the backing and the localizer from the fabric. Discontinuity of the backing (solid lines 519) underlying the tabs would also simplify removal of the fabric from-the backing and perforations through the backing (dotted lines 520) would facilitate separation of individual units from each other. If desired, a smaller diameter (e.g. 1 cm) ring and associated backing albeit without tab could be placed within the central space (21) bordered by the simple ring fabric 519.

[0074] Embodiments of a prefilled or fillable cross shaped localizer grid 600 are illustrated in FIGS. 15A-15F. In FIG. 15A, a modified tubular square 621 with diagonal dimensions of 2 cm and containing 2 smaller caliber spokes 623 at right angles to each other serves as the hub. Uniquely positioned rows of tubing (24) radiate from each corner along the vertical and horizontal axes. The luminal diameter of the radiating tubes is uniform and on the order of 2 mm. except where indicated by dotted lines 625 corresponding to gradual tapering from 0 to the uniform diameter. Depending on the distance from the central hub, with 1 or 2 rows of tubing will be present with up to 4 tubes in each row as best illustrated in a table of FIG. 15B. The lower row of tubes (i.e. closest to skin) would correspond to increments of 1 cm. and the upper row to increments of 5 cm so that a maximum distance of 24 cm would be denoted by 2 full rows. To indicate positive distances, the tubes are progressively ordered from left to right or down to up with the reverse true for negative distances as illustrated in FIGS. 15A-15B. Fractions of a centimeter would be indicated by the diameter of a cross section through a tapered portion of tubing divided by the full uniform diameter.

[0075] The cross-shaped grid of tubing is reversibly affixed to a medical grade adhesive fabric 626 with corresponding markings and backing. The fabric 626 is illustrated in FIG. 15C with the overlying tubing removed. The grid and associated fabric may come as a single cross-shaped unit or as a modified square and separate limbs which could be applied to the patient individually or in various combinations. Modified squares could also link whole units and/or individual limbs together to expand coverage, with 25 cm. spacing between the center of adjacent squares. The tubing may be flexible to allow the limbs to conform to curved body contours such as the breast. Additionally, either the limbs could be readily truncated at 5 cm. intervals or be available in various lengths for optimal anatomic coverage.

[0076] To add further utility and integration with the previously described point localizers, a modified ring may serve as the hub of the cross-shaped grid with associated modification of the limbs as illustrated in FIG. 15D. The orthogonal limbs would not have to maintain a coincident relationship to the spokes as with

the modified square hub. Rather, by first placing and rotating a calibrated ring adapter (FIG. 15E) about the modified loop, 1 to 4 limbs could be readily positioned at any desired angle relative to the spokes. Pairs of male plugs 627 extending from the ring, adapter would fit securely into corresponding holes 628 at each limb base to ensure proper positioning. It is foreseen that one would typically align the modified ring's spokes with the scanner's axes and the ring adapter/limbs with the axes of the body part to be studied. By noting the chosen angulation marked on the ring adapter, optimal scanning planes might be determined prior to imaging.

[0077] For planar radiography, a cross-shaped grid of radiopaque (e.g. lead or aluminum) dots at 1 cm intervals interposed by 5 cm spaced dashes (FIG. 15E) would minimize the imaging area obscured by overlying radiopacity. The minute opacities could be reversibly affixed by clear tape to an underlying marked adhesive fabric similar to that illustrated in FIG. 15C. Alternatively, in FIG. 15F similarly spaced radiopaque dots and dashes could be dispensed reversibly affixed to a role of medical grade adhesive tape with corresponding markings. Any length of this dually marked taped could be applied to the patient to include a single dot as a point localizer.

[0078] In a planar localizer grid/phantom 700, 1 cm spaced horizontal and vertical tubes form a graph paper-like lattice as illustrated in FIG. 16A. Tubes at 5 cm intervals (29) would have larger luminal diameters (e.g. 3 mm) than the others (e.g. 2 mm). Central vertical 730 and horizontal 731 tubes would have a smaller diameter (e.g. 1 mm). Overlying the lattice at a 45 degree angle is a slice indicator tube 732. Depending on the distance from the horizontal or vertical axes respectively, axial or sagittal cross sections through the grid/phantom (GP) would demonstrate the slice indicator tube 732 uniquely positioned as it overlies a row of 1 cm spaced tubes. FIG. 16B illustrates a representative axial slice obtained 6 1/2 cm above the horizontal axis. Note that the cross section of the slice indicator is positioned above and midway between the sixth and seventh tubes to the right of the sectioned vertical axis 730. Additionally, the thickness (t) of the image section can be readily determined as it equals the cross-sectional width (w) of the

indicator minus the square root of 2 times the diameter (d) of the indicator lumen,(t = w -V2" d).

[0079] The GP may be reversibly affixed to an adhesive/plastic sheet with a corresponding graph paper-like grid for skin marking and to serve as a sterile interface between the patient and GP. Perforations 733 may be placed in the sheet as shown in FIG. 16A to allow ready separation of a cross-like ruled adhesive fabric (similar to that illustrated in FIG. 15C), from the remaining plastic sheet after imaging and removal of the GP.

[0080] The square GP should have outer dimensions equal to a multiple of 10 cm (e.g. 30 cm as illustrated) to allow for simple computation if GPs are placed side to side for expanded surface coverage. Adapters could be provided to ensure secure and precise positioned of adjacent GPs either in plane or at right angles to each other. The GPs can be flexible or rigid in construction and be utilized with or without skin adhesion and marking.

[0081] Tubes may be filled uniformly or with a variety of known solutions having different imaging properties to serve as multipurpose references. For the latter, the 5 cm spaced tubes and slice indicator may be filled with the same optimized solution as previously described, while each set of 4 intervening tubes could be filled with different solutions in similar sequence. In this fashion, identical series of 5 reference solutions would repeat every 5 cm, allowing intraslice signal homogeneity to be assessed as well. If 9 rather than 5 different solutions are desired, sequences could instead be repeated every 10 cm. For MRI, the central tubes may also be surrounded by an oil/lipid within a larger lumen tube to serve as both a lipid signal reference and allow for measurement of the fat/water spatial chemical shift. Furthermore, if the GP tubing is surrounded by a perflurocarbon or other substance without magnetic susceptibility, MR imaging could be improved by reducing skin/air susceptibility artifact and dampening motion. The GP may also be incorporated into a variety of nonmodality specific pads (including the ubiquitous scanner table pad(s)), binders, compression plates, biopsy grids and assorted stereotaxic devices.

[0082] Two additional variations are now described, potentially replacing the somewhat complex cross design (FIGS. 15A-15F) with an extension of the basic point localizer (FIGS. 14A-14I) or modification of the planar phantom/localizer (FIGS. 16A-16B). These changes may further simplify and unify the proposed marking system.

[0083] In the first instance, rather than packaging the ring localizers in a sheet as illustrated in FIG. 14I, they could be packaged in a strip or roll 800, regularly spaced at 5 cm or other intervals (FIG. 17). The strip 800 with attached ring and/or cross localizers could then serve as a linear reference of any desired length. By placing two strips orthogonally, a cross-shaped grid is created. Individual rings can be removed from the strip or rotated to customize the grid as desired (FIG. 18).

[0084] In the second instance, by slightly modifying the square design illustrated in FIGS. 16A-16B, an elongated rectilinear or cross configuration (FIG. 17A) is achieved consisting of linearly arranged squares extending vertically and/or horizontally from the central square. One tube in each of these squares will have a larger diameter than the other similarly oriented tubes as determined by the square's distance from the isocenter. For example, the square centered 10 cm above the isocenter would have its first tube situated to the right of midline given an increased diameter and the square centered 20 cm above the isocenter would have its second tube to the right of midline given an increased diameter and so on.

[0085] Cross sectional distance from isocenter would be read by adding the distance determined by each square's diagonally oriented slice indicator to 10 times the numberline position of the largest diameter tube. FIG. 8B illustrates the cross sectional appearance of an axial section obtained 12 1/2 cm. above isocenter. By adding 2 1/2 (the slice indicator position) to 10 times 1 (the tube with largest diameter), distance is readily determined.

[0086] Alternatively, the caliber of all tubes could be kept constant and instead an additional diagonal indicator tube passing through isocenter added for each elongated axis (vertical with slope of 10 and horizontal with slope of 1/10). Cross-

sectional distance from isocenter would then be determined by looking at the position of both the additional and original diagonal indicator tubes in reference to the cross sectionally-created number line.

[0087] It should also be noted that localizer grids similar to those illustrated in FIGS. 16A-16B and 18 could be constructed of barium (or other high x-ray attenuative material) impregnated sheets rather than tubes if computed tomography is the primary imaging modality desired and phantom attenuation values are not needed. This would significantly reduce the cost of the grid, allowing disposability and retaining 1:1 compatibility with the multifunctional tube filled grid/phantom.

Flexible Phased Array Surface Coil With Integrated Multimodality, Multifunctional Spatial Reference And Skin/Surface Marking System.

[0088] It should be further noted that applications consistent with the present invention may be modified to include a sheath for and inclusion of a flexible array MRI surface coil. Positioned vertically, this device could be closely applied to the entire cervical, thoracic, and lumbar-sacral spine. Additionally, the quantity of tubes which need to be filled in the planar configuration to uniquely denote cross-sectional positioning, has been substantially reduced from the original embodiment.

[0089] Phased array surface coils significantly increase signal to noise in MRI and are commonly employed for spine imaging. Currently, such spine coils are rigid and planar in configuration. As such, patients can only be effectively scanned in the supine position, lying with the back against the coil. This results in signal drop-off in regions where the spine/back is not in close proximity to the planar coil, particularly the lumbar and cervical lordotic regions. The invention, described herein, would reduce the signal drop-off and allow patients to be scanned in any position. The prone position, for example, would facilitate interventional spine procedures that could not be performed with the patient supine. Patients could also be more readily scanned in flexion or extension; or with traction or compression devices. Current surface coils also lack an integrated spatial reference and skin marking system. Inclusion of the proposed spatial reference and skin marking system would facilitate multi-modality image fusion

and registration as well as the performance of diagnostic or therapeutic spine procedures, such as biopsies, vertebroplasty, or XRT.

[0090] A grid-localizer would be adhered to the patient's spine. Tubing would be filled with a MRI readily-visible solution such as water doped with CuSO4. The grid itself would typically be 10 cm wide and 70-90 cm in length to cover the entire spine. An attached clear plastic sheath would allow introduction of a flexible array coil such as illustrated in FIG. 9B.

[0091] The configuration of tubing would allow unambiguous determination of the MRI scan plane (axial or sagittal) in reference to the patient's back/skin surface. The number of thin caliber tubes could denote the distance from (0,0) in multiple of 10 cm as illustrated in FIG. 9B (those to the right or superior would be positive; those appearing to the left or inferior would denote negative distances). Alternatively, as illustrated in FIGS. 9C-9D the integer distance in centimeters from a single thin tube to the central tube could be multiplied by ten to denote distance from (0,0). Thus, 30 cm could be denoted by a single thin tube 3 cm from the central tube rather than by 3 thin tubes as in FIG. 9B. As illustrated in FIGS. 9C, 9D, an axial slice taken 8 cm superior to (0,0), would reveal the cross sectional tubes illustrated in 6d. The thin tube being 1 cm to the right of the central tube would denote a vertical distance of 10 cm. The diagonal oriented tube in cross-section, being 2 cm to the left of the central tube, would denote a vertical distance of -2 cm. Thus, the axial plane of section would be 10-2=8 cm above (0,0).

[0092] Using the described reference/marking system affixed to the patient's back, a diagnostic or therapeutic procedure could be performed under direct MR guidance. Alternatively with a corresponding radiopaque grid affixed to patient's back, the patient could be taken out of MRI scanner and have the procedure done with CT or fluoroscopic guidance. In either case, procedures could be performed by hand or with a robotic arm.

[0093] **Algorithms for identifying and characterizing discs and vertebrae.** A fast rule-based spine contour extraction method has been developed. It consists of the

following steps: (1) locating inter-vertebral disc locations; (2) finding the inter-vertebral contour using a deformable contour model; and (3) locating the vertebral boundary and the spine contour. This method enables automated scan prescriptions, real-time lesion detection, and examination tailoring.

[0094] Recent advances in MRI to include the clinical implementation of phased array-coils and parallel sensitivity encoded imaging offer the potential for time and cost effective non-invasive holistic screening and detailed assessment of neuro-axis pathology, to include stroke and back pain--both leading causes of disability in the U.S. However, optimal patient evaluation requires individually optimized MRI sequencing, which in turn requires real-time analysis of increasingly complex and multi-parametric MR data. The development and integration of an automated system emulating/approximating detailed expert analysis while the patient is still in the magnet would significantly improve diagnostic imaging and medical care. Millions of MRI scans are performed each year, approximately 65% dedicated to the evaluation of the brain and spine. Software to synergistically improve the prescription and analysis of such scans has tremendous commercial potential. No such product is currently available and would be of great interest to both large medical imaging companies engaged in computer assisted medical imaging diagnosis.

[0095] **Medical Applications -- Detection and Analysis of Brain Pathology with MRI (Acute Stroke, Intracranial Aneurysms).** At UC Medical Center, Talairach referenced axial diffusion-weighted images (DWI), whether prescribed by a technologist or a computer, are currently obtained following the initial roll and yaw corrected sagittal T2 sequence. If computer image analysis of the initial DWI sequence suggests regions of acute infarction, the basic brain protocol would be streamlined and modified to include MR angiography and perfusion sequencing. This would respectively permit evaluation of the underlying vascular lesion and the detection of potential perfusion/diffusion mismatches directing emergent neuro-vascular intervention. Stroke is the leading cause of disability in this country. Because the time to emergent therapy strongly inversely correlates

with morbidity and mortality, the development and implementation of the proposed computer algorithms could significantly improve patient outcome.

[0096] In conjunction with the Mayo Clinic, researchers at UC Medical Center are currently studying a large population of patients at risk for intra-cranial aneurysms using MR angiography. One of the investigators (Dr. Weiss) has developed and implemented co-registered white and black blood MR angiography sequences which uniquely facilitates computer-aided diagnosis and analysis of potential aneurysms in this population. In the proposed work, such computer algorithms will be developed and their sensitivity will be compared against the expert standard (3 independent euroradiologists' assessments already in place). If computer image analysis of such initial MRA screening sequences reveals a potential aneurysm, dedicated phase-contrast images of the putative aneurysm could be iteratively prescribed to better characterize the lesion and assess flow characteristics.

[0097] Using computer flow modeling and other engineering analysis, the investigators plan to better stratify an individual aneurysm's risk for rupture, This could lead to more optimized patient management as the majority of brain aneurysms do not rupture and therapeutic intervention (coiling or clipping) carries morbidity and mortality risks. Tobacco smoking significantly increases the incidence ischemic brain disease as well as aneurysms and their rupture leading to catastrophic stroke.

[0098] **Detection and Analysis of Spine Pathology with MRI (Fractures, Disc Herniations).** Spine pathology is another leading cause of disability in this country. The proposed research will improve detection and assessment of disco-vertebral degeneration, osteoporotic and pathologic compression fractures-all potential underlying causes of ubiquitous back/neck pain in this country.

[0099] Using advanced MR imaging techniques, the entire spinal axis can be interrogated in the sagittal plane in less than a minute. With this screening data, the vertebral bodies and inter-vertebral discs can be identified and subsequently analyzed with the software proposed for development. Based on this initial

assessment, regions of suspected pathology to include vertebral fractures and disc hernations, could be further interrogated with more dedicated computer driven prescriptions to confirm and better characterize pathology. If for example, a fracture is identified, additional multiparametric sequencing through the involved vertebrae would be obtained to determine whether the fracture was related to osteoporosis or underlying malignancy.

[00100] In conjunction, with the aforementioned software to iteratively prescribe and analyze brain MRI, the entire neuro-axis can be effectively screened and lesions characterized in a single time-efficient scan session. Currently, such an examination is prohibitively lengthy and requires several imaging sessions if lesions were to be optimally characterized. Image analysis development for this MRI project should be synergistic with that done for the X-ray evaluation of vertebrae in the following section.

[00101] **Automated Spine MRI for Rapid Osteoporosis Screening.** With the spine labeled and imaged, further analysis is then enabled for diagnosing conditions of the spine. Novel MRI technique provides efficient screening and iterative assessment of patients at risk for osteoporotic spine fractures. In particular, refinement of the above-described Automated Spine Survey Iterative Scan Technique (ASSIST) to optimize sub-minute morphologic screening of entire spine with MRI; (2) to combine technique with investigational 3-point Dixon methodology to provide quantitative assessment of vertebral marrow fat fraction (F%) and cancellous bone-induced intravoxel spin dephasing rate (R2*); and (3) to perform multi-variate analysis to model vertebral fracture risk as approximated by #1, with F%, R2*, and spinal dual-energy x-ray absorptiometric (DEXA) bone mineral density (BMD).

[00102] Osteoporosis is a disease characterized by low bone mineral density and abnormal bone microarchitecture. Currently, it affects about 30% of post-menopausal women, with more than 50% at risk. With our population rapidly aging, the prevalence of osteoporosis continues to rise. As osteoporotic-related fractures result in major morbidity, health care expenditures, and mortality in the

elderly, this proposal addresses the DDF's desire to promote research in Aging-Geriatrics. Moreover, by applying cutting-edge investigational technology to this critical health-care problem, the study fulfills Translational Research Initiative goals as well.

[00103] The traditional criterion for assessing fracture risk is bone mineral density (BMD) as may be measured by single-photon absorptiometry (SPA), quantitative computed tomography (QCT), single-energy x-ray absorptiometry (SXA), and most commonly dual-energy x-ray absorptiometry (DEXA). Unfortunately, while negatively correlated with fracture risk, BMD by itself remains an unsatisfactory predictor. Consequently, investigational work has increasingly focused on ultrasound and MRI. The latter technique has the unique potential to quantify fractures, which are highly correlated with subsequent risk of fracture; differentiate between osteoporosis and other underlying pathology, such as metastases; and target therapy such as vertebroplasty. MRI researchers have also demonstrated improved fracture risk prediction by combining DEXA measurements with Dixon sequence derived F% (positively correlated) and R2* (negatively correlated). Unfortunately, MRI of the spine has been too time intensive and costly to justify as an osteoporosis-screening instrument.

[00104] To rectify this important shortcoming, integration is made of the 3-point Dixon technique with our novel automated sub-minute sub-millimeter resolution total spine screen. This should afford rapid high-resolution morphometric assessment, as well as, the separation and quantification of fat, water, and R2*. We plan to test this methodology on 50 post-menopausal women who have been referred for a DEXA scan.

[00105] In particular, a novel MRI technique improves current screening, assessment, and surveillance of the elderly at risk for osteoporotic spine fractures. As osteoporotic fractures result in major morbidity, health care expenditures, and mortality in the geriatric population, this proposal directly addresses the Dean's Discovery Fund's desire to promote research in Aging/Geriatrics. Moreover, by

applying cutting-edge investigational technology to this critical health-care problem, the study fulfills Translational Research Initiative goals as well.

[00106] Osteoporosis and related fractures are a leading cause of morbidity, disability, decreased quality of life and mortality in the aged. (2-4) The wide range of therapeutic options available for prevention and treatment require effective screening, assessment, and monitoring of geriatric patients at risk for osteoporotic fractures. Conventional measurements including bone mineral density (BMD) analysis are imperfect predictors of fractures. (4) MRI-derived parameters hold promise for improved risk prediction and fracture evaluation. (5) Unfortunately, MRI has been too time intensive and costly to justify as an osteoporosis-screening instrument. To rectify this important shortcoming, we propose refinement and integration of MRI derived parameters of bone quality with our novel rapid high-resolution total spine screen (1) The long term goal is to promote geriatric patient care by providing improved risk assessment, identification and characterization of fractures.

[00107] The central hypothesis is that our computer automated MRI technique will efficiently screen and assess elderly post-menopausal women at risk for osteoporotic spine fractures. More specifically, our multi-parametric approach will 1) improve fracture risk prediction and 2) accurately identify and characterize existing fractures. The following specific aims will be pursued to test this hypothesis:

[00108] Improve vertebral fracture risk prediction: MRI derived measurements of vertebral morphology and bone quality (fat fraction, F%; transverse relaxation rate, R2*) will be calculated for each vertebra. These parameters will be analyzed in conjunction with standard dual-energy x-ray absorptiometric (DXA) to develop a model for prediction of vertebral fracture risk.

[00109] Accurately identify and characterize existing vertebral fractures: Our novel MRI Automated Spine Survey Iterative Scan Technique (ASSIST) will be adapted to provide automated morphologic assessment of vertebrae and detect

vertebral fracture deformities. This functionality will be compared to lateral thoracolumbar x-ray, which currently serves as the clinical standard.

[00110] Osteoporosis is an important geriatric health issue and poses a most serious public health problem. With life expectancies increasing, the financial and human costs associated with osteoprotic fractures will multiply exponentially throughout the world. Vertebral fractures are strongly correlated with age (mean 65 years) but even more so with menopause. In the United States, one out of two women and one in four men over age 50 will have an osteoporosis-related fracture.

[00111] Osteoporosis is a metabolic disease characterized by low bone mineral density and abnormal bone microarchitecture increasing fracture risk. The traditional criterion for assessing fracture risk is bone mineral density (BMD) as may be measured by single-photon absorptiometry, quantitative computed tomography, single-energy x-ray absorptiometry, or most commonly dual-energy x-ray absorptiometry (DXA). Unfortunately, while negatively correlated with fracture risk, BMD by itself is not a perfect predictor.

[00112] Fractures are the ultimate manifestation of lost bone structural integrity. One fractured vertebra increases the risk of subsequent vertebral fracture 5-fold. Consequently, low resolution morphometric x-ray absorptiometry and/or more precise high resolution conventional thoracolumbar spine x-rays are often ordered to supplement BMD measures. Vertebral fractures are commonly assessed on x-rays semiquantitatively and reported using Genant's 0-3 grading scale with grade 1 corresponding to a fracture deformity of 20-25%. More mild deformities are typically not scored but are also somewhat associated with lower BMD and increased fracture susceptibility.

[00113] Conventional radiography, however, has several shortcomings in the detection of vertebral fractures. Different technical parameters in the acquisition of lateral spine radiographs influence vertebral dimension measurements, thus degrading reproducibility, especially in scoliotic patients. Vertebral body outlines are more difficult to visualize on x-ray in the population most at risk for osteoporotic fracture due to their reduced BMD. Radiographs also have limited ability to

assess fracture chronicity, etiology, or potential effectiveness of targeted intervention to include vertebroplasty or kyphoplasty. Moreover, ionizing radiation from serial radiographic examinations must be taken into account, especially when considering clinical trials typically requiring numerous exposures.

[00114] Consequently, investigations have increasingly focused on ultrasound and MRI. MRI has the unique potential to simultaneously quantify fractures; differentiate between osteoporosis and other underlying pathology, such as metastases; and appropriately target therapy such as vertebroplasty. Additionally, spinal MRI affords direct visualization of the intervertebral discs, spinal canal, bone marrow, and neural tissue. MRI can accurately quantify vertebral morphology. Cyteval and colleagues have recently demonstrated the accuracy and reproducibility of MRI for the determination of vertebral body dimensions. They also found that the sagittal midline area was highly correlated with whole vertebral body volume and that each vertebra was proportional to other vertebrae in the same individual.

[00115] MRI can also provide bone quality measurements related to osteoporosis. MRI researchers have demonstrated improved fracture risk prediction by combining DXA measurements with Dixon sequence derived fat percentage—F% (positively correlated) and transverse relaxation rate—R2* (negatively correlated). When trabeculae are not aligned with the magnetic field, susceptibility differences at the interface between trabecular bone and bone marrow increase R2*. Consequently, R2* measurements reflect both trabecular bone structure and orientation.

[00116] The Dixon technique exploits the resonant frequency differences between fat and water to separate the water signal intensity from the fat signal intensity. This frequency difference is measured as a phase difference in the acquired data. Acquisition of three separate measurements or Dixon echoes allows generation of a water image, a fat image, and a magnetic susceptibility map from which F% and R2* can be derived. (6)

[00117] To date, while promising, MRI examinations have been too time intensive and costly to justify for osteoporosis-screening. To rectify this important shortcoming, we propose integration of the three-point Dixon technique with our novel automated sub-minute sub-millimeter resolution total spine screen. This should afford rapid high-resolution assessment of both vertebral morphometry and bone quality.

[00118] Rapid Osteoporosis Screening: Sagittal FGRE (TR 58; TE 2.1; 30° flip; 7 slices; 4 mm skip 1 mm; 35 cm FOV x 2 = 70 cm) with contiguous superior and inferior stations. The imaging parameters have been selected to emphasize contrast between vertebral discs and bodies with full coverage from the cervical spine through the sacrum in 42 seconds.

[00119] Three-Point Dixon Technique: Sagittal FSE Dixon (7 slices; 4 mm skip 1 mm; 44 cm FOV) covering T4-S1 and prescribed using the superior ASSIST station as localizer. The Dixon technique exploits molecular resonant frequency differences between fat and water to produce high resolution fat, water, and transverse relaxation rate (R2*) images.

[00120] While the present invention has been illustrated by description of several embodiments and while the illustrative embodiments have been described in considerable detail, it is not the intention of the applicant to restrict or in any way limit the scope of the appended claims to such detail. Additional advantages and modifications may readily appear to those skilled in the art.

[00121] What is claimed is: